REMARKS

Claims 1, 3-8 and 10-54 are pending in the application. However, claims 25-43 and 48-54 have been withdrawn from consideration by the Examiner. Accordingly, claims 1, 3-8, 10-24 and 44-47 are pending and under consideration in the present application. Re-examination and reconsideration of the application is requested.

Applicant expresses appreciation to the Examiner (Ms. Pak) for the courtesy of the telephone interview conducted with the undersigned on September 2, 2004. In that telephone interview, the undersigned explained distinctions between the present invention and the Wohlfahrt et al. reference and other references applied in rejections of record. Applicant requests that the Examiner consider those remarks in conjunction with the following remarks and withdraw the rejections of record.

In particular, claims 1, 3-5, 19-24 and 44-45 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wohlfahrt et al. in view of Kenan et al. Claims 6-8 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wohlfahrt et al. and Kenan et al. and further in view of Byalina et al. Claims 10-16 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wohlfahrt et al. and Kenan et al. and further in view of Shtelzer. These rejections are respectfully traversed in view of the comments below and the telephone interview conducted with the Examiner (Ms. Pak) on September 2, 2004.

Similar rejections were raised in the Office Action dated December 17, 2003, and responded to in the Amendment filed on March 17, 2004. To address the present rejection, consideration is also given to the Examiner's statements in the December 17, 2003 Office Action.

In the Office Action of December 17, 2003, the Examiner stated that Wohlfahrt et al. and other references teach that glucose oxidases are susceptible to peroxide dependent inactivation (citing Wohlfahrt et al., pgs. 973-976; Greenfield et al., pg. 11 and Binyamin et al., abstract). However, each of those references is either silent regarding any manner of addressing peroxide inactivation or suggests a completely different approach than the direction of the present claims. None of those references describes or suggests a method of formulating an enzyme as recited in

claim 1 of the present application. In particular, none of the prior art of record, alone or in combination, describes or suggests a method as recited in claim 1, wherein colonies are grown and screened for active glucose oxidase (by measuring glucose oxidase concentration) and for peroxide resistant properties (by incubating the colonies in peroxide and determining whether the colonies have active glucose oxidase after incubation).

More specifically, the Examiner cited a large portion of the Wohfahrt et al. reference (pgs. 973-976 is about one-half of the entire article) which describes modeling glucose oxidase, but does not appear to describe or suggest any manner of addressing peroxide inactivation of glucose oxidase. Instead, Wohlfahrt et al. describe very different processes involving relatively complex modeling and simulations of specific enzymes.

Wohlfahrt et al. neither mention nor suggest (1) a peroxide resistant enzyme; or (2) a peroxide resistant enzyme capable of functioning in a biosensor environment (an oxygen deficient environment). While the Examiner state that Wohlfahrt et al. teach methods of decreasing susceptibility of glucose oxidase to oxidation by chemicals such as peroxides by generating mutants, Applicant found no portion of the Wohlfahrt et al. reference that describes decreasing susceptibility to peroxide. The desirability of a peroxide-resistant enzyme or a biosensor with a peroxide-resistant enzyme was not contemplated by Wohlfahrt et al. As such, Wohlfahrt et al. would not have led one of ordinary skill in the art to perform the methods recited in the present claims.

Greenfield refers to bactericidal effects of hydrogen peroxide. However Greenfield expressly acknowledged that "[l]ittle data exists concerning the effect of hydrogen peroxide on glucose oxidase." (Greenfield, pg. 11, ll. 2-4.) Binyamin et al. refer to damage to hydrogel films caused by "chemical attack by H_2O_2, an undesired by-product." To address that problem, Binyamin et al. teach to overcoat the enzyme film with a layer of immobilized catalase." (Binyamin et al., Abstract, ll. 6-8.) There is no suggestion of formulating an enzyme or biosensor, including screening colonies for active glucose oxidase and peroxide resistant properties, as recited in the present claims. Instead, Binyamin et al. teach away from the present method by teaching to address chemical attack of H_2O_2, by applying a catalase overcoat.

The directions taken by Wohlfahrt et al. and Binyamin et al. and the lack of action taken by others shows that the above-discussed references were not focused in the direction of the present invention and, instead, were focused in other directions. Thus, those references, alone or in combination, would not have led one of ordinary skill in the art to the claimed invention.

In the December 17, 2003 Office Action, the Examiner acknowledged that a difference between the teaching of Wohlfahrt et al. and the claimed invention is that "Wohlfahrt et al. does not teach a method for generating cDNA library and selectively screening for mutant galactose oxidases genes resistance against oxidation by peroxides and mutant galactose oxidase genes encoding active galactose oxidases." While acknowledging those distinctions over Wohlfahrt et al., the Examiner stated that "cloning and screening methods for mutants generated by mutagenesis is extremely routine and well known" and that "it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to screen colonies containing mutant glucose oxidases for a functional protein and one having resistance to oxidation by peroxide using the methods well known in the art." In the Office Action dated June 2, 2004, the Examiner stated that "Kenan et al. teach that a library of colonies can be generated and protein expression libraries can be screen for functional properties, for example, such as catalysis (cDNA Libraries, page 2)."

However, Kenan et al. neither describe nor suggest formulating an enzyme or biosensor, including screening colonies for active glucose oxidase and peroxide resistant properties, as recited in the present claims. The present claims include screening colonies, but employ such screening in a unique and non-obvious method. Regardless of whether library screening processes were known in the art, none of the prior art of record teach or suggest screening colonies for desirable properties by determining whether the colonies contain active glucose oxidase (by measuring a concentration of the glucose oxidase) and by determining whether the colonies have peroxide resistant properties (by incubating the colonies in peroxide and determining whether the colonies have active glucose oxidase after incubation).

Instead, references cited by the Examiner for suggesting that glucose oxidase is susceptible to peroxide teach wholly different approaches involving complex modeling and

simulation of specific enzyme properties or applying catalase film overcoats. Those references would have taught one of ordinary skill in the art in directions away from the direction of the present invention. Furthermore, if library screening processes were "extremely routine and well known," then the fact that such routine and well known screening processes were not mentioned at all by any of those references cited by the Examiner for teaching susceptibility of glucose oxidase to peroxide (i.e., Wohlfahrt et al., Greenfield and Binyamin et al.) is further evidence that those references were focused in different directions than methods involving screening of colonies, as claimed.

Moreover, the method recited in claim 1 of the present application can provide significant advantages over such references as Wohlfarht et al., Greenfield and Binyamin et al. The ability to form a stable enzyme which is peroxide resistant and which may be employed in an altered environment (oxygen free environment), such as a biosensor, can provide significant advantages in extending the life of biosensors. When used in an implanted medical device (such as an implanted blood glucose sensor), peroxide resistance and, thus, a capability for extending the life of the enzyme can provide considerable patient comfort and safety advances, for example, by reducing the frequency of surgical sensor replacements. Moreover, the ability to form enzymes with peroxide resistant properties suitable for biosensor applications in a relatively inexpensive, non-complicated and reliable process can provide significant advantages with respect to the ability to manufacture readily available supplies of the enzyme and, thus, increasing the availability of longer-life biosensors to more patients.

Had the presently claimed method been obvious over the prior art of record, then such significant advantages would have led the authors of those prior art references to at least mention the possibility of performing such methods. However, no such disclosures were made in the cited references. Thus, the significant advantages available with the present invention, as compared to the processes described in the prior art of record, shows that the presently claimed invention is not obvious over the prior art of record.

Therefore, it is respectfully submitted that, without the present disclosure as a guide, it would not have been obvious to combine Wohlfahrt et al. with Kenan et al. to arrive at the

invention recited in claim 1. Neither the Byalina et al. nor the Shtelzer references address the above-noted distinctions of the present claims over the Wohlfahrt et al. and Kenan et al. references. Accordingly, the rejection of claim 1 and the rejections of dependent claims 3-8, 10-24 and 44-47 are respectfully traversed.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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